Remarks

This paper is in response to the Office Action of February 6, 2004, due on or before May 6, 2004. Applicant believes this Amendment and Response to be timely, and believes that no additional extension fees are due.

Claims 32, 35-40, 42 and 43 are hereby cancelled without prejudice. Applicant preserves the right to pursue these claims, including claims of broader scope where permissible by law, in related applications.

New claims 44-59 are hereby submitted for examination. No new matter is introduced by these claims. Support for these new claims is found in the claims as originally filed and the specification, and is discussed in more detail within the context of the prior art rejections, addressed below.

Rejections Under 35 U.S.C. §112, Second Paragraph, Overcome.

Applicant has cancelled claims 32, 35-40, 42 and 43, and believes this moots any rejection under 35 USC 112, second paragraph. Accordingly, Applicant requests withdrawal of this rejection.

Rejections Under 35 U.S.C. §102(b), Overcome.

Prior pending claims 32, 35-40, 42 and 43 stood rejected under 35 USC 102(b) as being anticipated by each of the following, Wright et al., Stevenson et al., Chen et al. (1994) and Chen et al (1996). Applicant traverses each rejection in view of the claims as amended. Accordingly, Applicant requests withdrawal of these four rejections.

Applicant has discovered a gene therapy approach to providing therapeutic polypeptides to a subject. Applicant states in paragraph 1 of the Specification:

> The present invention concerns the area of gene therapy comprised of transferring into the cells of a subject at least one gene coding for a

> therapeutic protein. More specifically, the invention concerns the transfer, into cells not normally producing antibodies, of nucleic acid sequences coding for all or part or a derivative of therapeutic antibodies involving a protein component participating in the therapeutic effect, so that the cells genetically modified by these nucleic acid sequences and incorporated in a subject produce and secrete in the blood circulation of said subject a therapeutically effective quantity of this antibody.

Applicant was the first to recognize that immunoglobulins and their fragments could be expressed in *cells not normally producing* these polypeptides. It is submitted by the Office, and Applicant agrees, that one skilled in the art, as evidenced by Wright et al, Stevenson et al, and Chen et al (1994) and (1996) would know how to express immunoglobulins by recombinant means, including fragments, humanized and chimeric antibodies, etc. In fact, immunoglobulins had proven surprisingly adaptable to the tools of molecular biology, and many types of hybrids and fusion proteins had been developed prior to the filing date of this application. Likewise, many expression systems were known, permitting researchers to, for example, affect glycosylation of an antibody produced by recombinant means, or to use regulatable or inducible promoters for tissue specific or other types of controlled expression of recombinant proteins.

Nevertheless, while it was known to use mammalian cells for antibody expression systems as evidenced by Wright et al., and Chen et al (1994 and 1996), these papers all discuss transforming with the particular therapeutic gene, cell lines that are all immortalized. Wright et al. discloses using HeLa cells as expression vehicles. These are carcinoma cells. Chen et al (1994 and 1996) disclose using COS cells and MOLT-4 cells; COS cells are immortalized monkey cells subject to BL-2 handling precautions by ATCC; and MOLT-4 cells are leukemic. Stevenson et al. discloses a naked DNA vaccination approach, and does not disclose transplantation of a genetically modified cell, as the cells in Stevenson et al., are themselves transfected.

Applicant states in paragraphs 50, 52 and 53 of the Specification:

> The biological material of the invention is used in the preparation of pharmaceutical compositions for the treatment or prevention of cancer relapse, and viral infection or spread, AIDS in particular... Serious viral diseases are increasingly affecting human populations, in particular, of course, the AIDS virus, for which there currently is no effective means of preventing or treating infection. The biological material of the invention is significant in that it permits us to consider a new therapeutic approach for these very serious diseases.

Thus, Applicant's stated objective is the *prevention and treatment of disease*, specifically cancer and viral infections. Paragraph 54 of the Specification continues:

> In fact, in the case of cancer, it would permit the organism to use over the long-term specific antibodies of tumor cells, either cytocides, or those inducing cellular dormancy. This goal is reached in using nucleic acid sequences carrying a gene coding for antibodies directed against a specific tumor cell antigen.

Accordingly, Applicant recognized that a gene therapy approach could be used to deliver therapeutic antibodies for treatment of disease, e.g., cancer. This approach was not limited to cancer, as Applicant was aware of attempts to use gene therapy in the prevention and treatment of several diseases, including those of a viral nature. Chen et al., 1994 and 1996, and Stevenson et al. each support the premise that one of skill in the art would consider using antibody-based therapies against viral diseases, and even that a gene therapy approach at delivering antibodies is desirable. Applicant was aware of specific gene therapy approaches to therapeutic vaccination against certain viral diseases and cancers, specifically influenza and lymphoma, and he refers to these approaches in paragraphs 14 -17 of the Specification:

> Substances capable of interfering with pathology and which we attempt to produce in the patient's organism for gene therapy include certain antigens

> or antibodies. The expression of DNA sequences coding for antigenic proteins aims to permit the production, by cells genetically modified by this DNA, of antigens capable of inducing immunization of the individual. Such a vaccination strategy has, for example, been implemented in the case of different pathogens including the influenza virus (Tang, D., De Vit, M., and Johnston, Nature, 356 152-154, 1992). The in vitro production of antibodies, fragments of antibodies or derivatives of antibodies such as chimerical antibodies, by genetic engineering in eucaryotic cells has also already been described, for example, in European patents published under numbers 120 694 and 125 023. The injection into patients of therapeutic antibodies aims to target antigens involved in pathology in order to neutralize either directly, or through a chain of metabolic or immune events, one of the causal agents of the disease. Examples of such therapeutic strategies include treatment or prevention of B lymphomas (Yefenof, E., Picker, L. I., Scheuermann, R. N., Vitetta E. S., Street, N. E., Tucker, T., Uhr, J. W., Current Opinion in Immunology, 5, 740-744, 1993). The international patent application published under No. WO 94/29446 describes the intracellular expression of DNA sequences coding for antibodies. This approach permits considering direct in vivo gene therapy for pathology involving cellular components which are not accessible with traditional vaccination methods or based on the in vivo production of recombinant antigens. The DNA sequences expressed by the genetically modified cells in accordance with the method described in the international patent application WO 94/29446 are therefore essentially characterized by the fact that they include an antibody gene modified so that the antibody is not secreted.

Chen et al (1994 and 1996) both teach that a gene therapy approach is desirable to the prevention and treatment of HIV infections, but these references disclose using leukemic cells that express anti-gp120 antibodies in an *in vitro* assay. This supports Applicants assertion that he was aware of many possible therapeutic uses for the claimed invention, particularly in the treatment of viral infections, cancer, and hormone imbalance (as described in paragraphs 68 and 69 of the Specification), and

the principle that one skilled in the art understood how to make and use mammalian expression systems for the production of recombinant therapeutic antibodies, and even that it might be desirable to use a recombinant expression system in a gene therapy approach (Chen et al., 1996). However, neither reference anticipates the claims as amended.

Applicant claims a genetically modified cell comprising a polynucleotide encoding an antibody or fragment thereof, and a promoter sequence controlling expression of the polynucleotide in the cell, wherein the cell expresses and secretes the antibody or fragments thereof, and wherein the cell is a non-plasmocyte mammalian cell suitable for introduction into a subject in that the genetically modified cell does not cause disease in the subject following transplantation. Wright et al, and Chen et al (1994) and Chen et al (1996) each do not anticipate the present claims, as they do not disclose either directly or implicitly, that the cell type used to express the polypeptide does not cause disease in the subject following transplantation. These papers (Wright et al, and Chen et al (1994) and Chen et al (1996)) each teach away from the claimed invention because each discloses cells that *ARE NOT* suitable for introduction into a subject and would have been understood to cause disease in the subject following their transplantation. Such a skilled artisan would have expected the use of COS, MOLT-4, or HeLa cells, as taught by Chen et al. (1994), Chen et al. (1996), and Wright et al., to cause tumors in the mice. The tumorigenicity of these cell lines is inconsistent with Applicants stated purpose of curative gene therapy.

Applicant indicates that following transplantation, the subject is monitored for emergence of disease. For example, Applicant monitors a transplant subject for the formation of a pathogenic autoimmune response to the Tg10 antibody produced and secreted by transplanted C2C12 cells in syngenic C3H mice. This is described in paragraphs 95 and 96 of the Specification:

> A possible risk of this approach is the induction of an immune response on the part of the modified organism capable of neutralizing the recombinant antibody. This potential problem was avoided in the experimental results presented below. $2x10^7$ primary myogenic cells expressing a stable Tg10 monoclonal antibody after retroviral transduction were implanted at the level of the tibialis anterior of the C3H mouse. The mouse serum was sampled at one week intervals for several months. The quantity of Tg10 antibody secreted was dosed with the ELISA method. In parallel, the quantity of anti-idiotype antibody was determined by ELISA.

Applicant monitored the transplant subject, describing in paragraph 97 the general health of the subject and results of assays for protein expression:

> In a series of 5 mice, secretion of Tg10 antibody was between 100 and 300 ng/ml of serum for 4 months. No anti-idiotype response could be detected under these conditions.

Applicant was (and one of skill in the art would have been) familiar with all appropriate protocols governing animal experimentation, in place at the time of filing. For example, one of skill in the art would have been obligated to monitor any mice receiving transplanted cells for the formation of any diseases, such as the development of tumors. Notably, animal welfare guidelines in place at this time would have required that any mice developing such tumors be euthanized within a reasonable period following tumor formation. Applicant would have been obligated to monitor the subject mice for any immune response as well as the formation of cancerous tumors, and in the Specification, Applicant describes monitoring the mice receiving the transplanted cells through the four month endpoint of the study. Thus, Applicant, and others skilled in gene therapy, would have understood that any gene therapy approach would require strict monitoring of the recipient subject for any pathogenic condition, for example, any uncontrolled or aberrant cellular proliferation of the transplanted cell, any pathogenic

immune response to the cell or to the immunoglobulin, and generally any other pathological condition resulting from transplantation of a cell or expression of a transgene.

Applicant describes the type of cells that are suitable for transplantation in accordance with the invention, and addresses the possibility of immunological rejection of the cell by the recipient subject. Paragraph 36 and 37 of the Specification recite:

> The cells not naturally producing antibodies entering into the composition of the biological material of the invention may derive from the mammal to be treated. In this variant, the cells are prepared using the traditional techniques of cellular and molecular biology, such as for example from biopsies taken from the patient to be treated. These cells are then genetically modified by the nucleic acid sequence carrying the antibody gene, either by transfection or infection with a vector conforming to those described above in the case of a direct in vivo gene transfer. Pharmaceutical compositions manufactured from this biological material are given back to the patient from whom the cells have been sampled. The cells not naturally producing antibodies entering into the composition of the biological material of the invention may derive from a human or animal mammal other than the one to be treated. These cells were prepared as in the preceding variant. In the case of cells of human origin, these cells come from compatible donors; in the case of cells of non-human origin, cells of genetically modified animals are used, such as the pig, made compatible for an organ transplant.

Likewise Applicant discusses in paragraphs 42-47 of the specification, that the cells are selected based on their suitability for incorporation into a mammal. The specific paragraphs read:

> More specifically, for the fourth potential embodiment of the invention, these cells are selected for their capacity to easily tolerate being sampled, genetically modified ex vivo and incorporated into a mammal. Among the cell types having the preceding characteristics, the invention relates more

specifically to keratinocytes, hepatocytes, skin fibroblasts, myoblasts, endothelial cells and hematopoietic stem cells. It has surprisingly been demonstrated (Fenjves, E. S., Smith, J., Zaradic, S., and Teichman, L. B., Human Gene Therapy, 5, 1241-1248, 1994) that the keratinocytes could relatively effectively produce proteins for the organism and not only for external use. In addition, they have been easily and routinely cultured for several years in hospital departments for skin grafts. Hepatocytes are more difficult to handle than keratinocytes. However, it has been demonstrated (Grossman, M., Raper, S. E., Kozarsky, K., Stein, E. A., Engelhart, J. F., Muller, D., Lupien, P. J., Wilson, J. M., Nature Genetics, 6, 335-341, 1994; Ferry, N., Duplessis, O., Houssin D., Danos, O., Heard J-M., Proc. Natl. Acad. Sci., USA, 88, 8377-8381, 1991) that hepatocytes can be infected by recombinant retroviruses both ex vivo and in vivo. Retroviral culture and transduction of skin fibroblasts is easy to do (Moullier, P., Marechal, V., Danos, O., Heard, J-M., Transplantation, 56, 427-432, 1993). Organoids are easy to handle (Moulier et al, Nature Genetics, 4, June 1993), 154-159). Fibroblasts have the advantage of being easy to sample in a subject by using a simple surgical procedure. In addition, gene therapy protocols are underway to correct lysosomal deficits in children. Myoblasts, which are undifferentiated muscle cells, can also be purified, and will likely be used without genetic modification for the treatment of certain degenerative diseases (Yao, S-N., Smith, K. J., and Kurachi, K., Gene Therapy, 1, 99-107, 1994).

Thus, one of skill in the art, in view of the guidance provided by paragraphs 42-47 of the Specification would never use an immortalized cell line, as these types of cells were well-known to be unsuitable for transplantation or for therapeutic human gene therapy, and were even prohibited from such uses by the applicable regulatory guidelines.

In view of the above, Applicant respectfully requests withdrawal of the four rejections under 35 USC 102(b) as neither Chen et al. (1994), Chen et al. (1996), Stevenson et al. or Wright et al. anticipates the claimed invention.

Conclusion

Applicant submits that the present application is in condition for allowance and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below. Applicant believes this Response to be timely, but the Commissioner is nevertheless authorized to charge payment of any filing fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-2678 (Reference No. 58256-010200).

Respectfully submitted,

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